REMARKS

Claims 1-37 are pending in the subject application. Claims 23-37 have been withdrawn from consideration. In the present Office Action, claims 1-22 stand rejected under 35 U.S.C. § 103(a). Specifically, claims 1-5, 13-15, and 22 stand rejected under 35 U.S.C. § 103(a) as being obvious over Goldman et al., ""Quantitative Double-Label Radiography of Two-Dimensional Protein Gels Using Color Negative Film and Computer Analysis," *Eur. J. Biochem.* 131, 473-480 (1983) ("Goldman") in view of U.S. Patent No. 5,268,486 to Waggoner et al. ("Waggoner"); claims 6 and 16 stand rejected under 35 U.S.C. § 103(a) as being obvious over Goldman in view of Waggoner and further in view of Potter, "A review of the CLIP system for the quantitative analysis of two-dimensional electrophoresis gels," *Electrophoresis*, 1990, 11, 415-419 ("Potter"); and claims 7-12 and 17-21 stand rejected under 35 U.S.C. § 103(a) as being obvious over Goldman in view of Waggoner and further in view of Anderson et al., "The TYCHO System for Computer Analysis of Two-Dimensional Gel Electrophoresis Patterns," *Clin. Chem*, 1981, 27(11), 1807-1820 ("Anderson"). In addition, the Specification has been objected to at several sites. Applicants respectfully traverse the rejection of claims 1-22 as set forth herein.

In the present Response, the specification has been amended at paragraphs [122] and [126] to present registered trademarks in capitalized format. Applicants submit that no new matter is added by these amendments.

Objections

In the Office Action, the Examiner has objected to the specification due to the format of trademarks presented in the application. Specifically, the Examiner has objected to CHAPS on pages 24 and 35, Superose on page 43, and Sepharose on page 44.

First, Applicants note that CHAPS is not a trademark but instead is an acronym for 3-[3(cholamidopropyl)dimethylammonio]-propanesulfonic acid. Therefore, pages 24 and 35 have not been amended herein.

Applicants have amended paragraphs [122] and [126] of the specification to change the format of the trademarks to all caps and indicating that the trademarks are registered with the USPTO (i.e., SUPEROSE® and SEPHAROSE®, respectively). No new matter has been added by these amendments. In view of the amendments to the specification, applicants respectfully request the withdrawal of the objection to the specification.

Rejections under 35 U.S.C. § 103(a)

Goldman and Waggoner

Claims 1-5, 13-15, and 22 stand rejected under 35 U.S.C. § 103(a) as being obvious over Goldman et al., "Quantitative Double-Label Radiography of Two-Dimensional Protein Gels Using Color Negative Film and Computer Analysis," *Eur. J. Biochem.* 131, 473-480 (1983) ("Goldman") in view of U.S. Patent No. 5,268,486 to Waggoner et al. ("Waggoner"). Applicants traverse this rejection for the reasons set forth herein.

In analyzing obviousness under 35 U.S.C. § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. See MPEP § 2141. In evaluating the differences between the prior art and the claims, the claimed invention as a whole must be considered, and the prior art must be considered in its entirety, including disclosures that teach away from the claims. See MPEP § 2141.02.

The analysis obviousness under §103 may be informed by attention to the following questions: a) whether there is some suggestion or motivation in the prior art to modify a reference or to combine the teachings of references; b) whether there was, at the time of the invention, a reasonable expectation of success that the modification or combination would work; and c) whether the prior art teaches or suggests all the claim limitations. See MPEP § 2143. Applicants submit that *prima facie* obviousness has not been established for at least the reasons that the cited prior art references do not teach or suggest all the claim limitations and there is no suggestion or motivation to modify the references. Thus there are differences between the prior art and the claims at issue. Applicants contend that those differences are substantial and non obvious.

Neither Goldman nor Waggoner, alone or combined, teach a matched labeling system for comparing protein compositions from at least two different samples utilizing a set of matched luminescent dyes chosen from dyes capable of covalently binding to proteins within said extract of proteins, wherein each dye within said set has a net charge which will maintain the overall net charge of the proteins upon such covalent binding and has ionic and pH characteristics whereby relative migration of a protein labeled with any one of said dyes is the same as relative migration of said protein labeled with another in said set.

Goldman discloses quantitative double-label radiography of proteins labeled with [^{3}H]-leucine and [^{14}C]-leucine. Proteins in *E. Coli* were radiographically labeled metabolically by growth of the cells in a medium containing one of the isotopes (Goldman, page 474, paragraph bridging the first and second columns). After mixing in a 10:1 ratio, the cells were separated on a two-dimensional gel. Emissions from the ^{3}H and spillover ^{14}C were recorded in one channel and compared to ^{14}C alone, which was recorded in a second channel (Goldman, page 474, column 1, second full paragraph). Since the emissions of the radiolabels are not equivalent (^{3}H maximum β energy emission of 0.0186 MeV and ^{14}C maximum β energy of 0.156MeV), protein samples containing different amounts of [^{3}H]-leucine compared to [^{14}C]-leucine were used to give a [^{3}H]-leucine to [^{14}C]-leucine ratio of 10:1 (Goldman, page 474, section entitled

"Labeling of Cells at Two Defined Growth Rates and Preparation of Cell Extracts"). Goldman does not match the radiolabels. The need to adjust the ratio to 10:1 evidences the marked distinction between the radioactivities of the two radiolabels.

The Goldman labeling system is not matched and the radiolabels do not bind to the protein. First, the radiographic labels have different emission energies and the protein ratios must be adjusted to correct for this difference. In the subject application, no such adjustments of the protein ratios are necessary. Further, there is spillover of ^{14}C-labeled leucine into the ^{3}H-labeled channel, so the labeled proteins cannot be effectively separated and quantified without a mathematical correction of the emission intensities. In addition, the labeled leucine must be incorporated directly into the protein during translation within the cell, whereas in the subject application an extract of proteins from each sample is prepared prior to labeling.

The Examiner acknowledges that Goldman does not teach the use of a matched set of dyes, but relies on the Waggoner patent to provide that teaching.[1] Applicants contend that the Waggoner patent also does not teach or suggest the use of a matched set of dyes.

Waggoner discloses water soluble luminescent dyes and methods for using those dyes. Although the Waggoner patent discloses generically that the dyes described can be used in multiparameter methods, the embodiment described in the paragraph bridging columns 3-4 does not separate the labeled proteins in the mixture. A plurality of dyes attached to a plurality of different primary components, such as antibodies, are added to a preparation containing secondary components, such as antigens, and then subjected to excitation wavelengths and viewed by means of a luminescence detection system, such as a flow cytometer or a fluorescent spectrophotometer. There is no teaching of matching dye characteristics and no

[1] *See*, however, pages 9-10 herein regarding the discussion of Related Applications in which the Examiner has previously concluded that the Waggoner patent does not teach the formation of a matched set of dyes "wherein the net charge, ionic characteristics and pH characteristics of the combined dyes are matched."

separation of the labeled proteins by electrophoresis or any other method. Moreover, because there is no eletrophoretic separation of the labeled proteins, there is no need to match the pH, ionic and charge characteristics of the dyes. Only the difference in the wavelengths is of concern in the multiparameter analysis described. Waggoner does not disclose creating a *matched set* of dyes wherein the dyes of the set have a *matched net charge* and *matched ionic and pH characteristics*, but emit luminescent light at detectably *different* wavelengths. Applicants do not disagree that the individual dyes presented in the Waggoner patent would possess characteristics, such as pH, net charge and emission spectrum under certain physical conditions. What applicants disagree with is that the Waggoner patent teaches the specific manipulation of those characteristics to create a *set of dyes* wherein the dyes within the set have certain characteristics that must be *matched* to those of the other dyes in the set and other characteristics that are not matched.

The claims of the present application do not claim multiple random dyes having random pH, net charge, ionic or light emission characteristics. The Waggoner patent discloses only that the light emission characteristics of different dyes may be manipulated to differ from other dyes used in the analysis. The Waggoner patent does not disclose *a set of matched luminescent dyes* having characteristics that are *matched* in a manner that ensures that any given protein in a protein sample will migrate the same as the same protein from another sample, regardless of which dye in that matched set is bound to that protein, and further that a protein from one sample that is not the same as a protein from the same or a different sample, will not migrate the same regardless of which dye in that matched set is bound to such different protein. In this way, one can be sure that the differences and identity observed in the migration of labeled proteins in a mixture of proteins from different sources are a measure of actual differences and identity in the proteins and not an error induced by differences in the characteristics of the dyes used to label the proteins. This is not a feature necessarily present in the multitude of dyes described in the Waggoner patent. This is not inherent in the dye combinations suggested by the Waggoner patent.

One having ordinary skill in the art would not be motivated by the disclosures of Goldman and Waggoner to develop a set of matched luminescent dyes. The Goldman method includes non-matched radiolabels having different emission energies which cannot be completely separated due to spillover, whereas Waggoner does not teach or suggest combining labeled proteins. Further, there is no teaching or suggestion that the radiolabels incorporated during translation within the cell can be replaced with labeling extracts of the proteins with a matched set of dyes of the subject application. Applicants submit that a case of prima facie obviousness has not been established and respectfully request that the rejection of claims 1-5, 13-15, and 22 be withdrawn.

Goldman, Waggoner, and Potter

Claims 6 and 16 stand rejected under 35 U.S.C. § 103(a) as being obvious over Goldman in view of Waggoner and further in view of Potter, "A review of the CLIP system for the quantitative analysis of two-dimensional electrophoresis gels," *Electrophoresis*, 1990, 11, 415-419 ("Potter"). Applicants traverse this rejection for the reasons set forth herein.

Potter discloses a computer method for analyzing images developed from a two-dimensional electrophoresis gel. However, as discussed herein, there is no teaching or motivation to combine the teachings of the Goldman reference with those of the Waggoner reference to give the methods of the subject application. Moreover, even if the teachings of the Goldman and Waggoner references were combined, they would not result in the subject matter recited in the claims of the present application. Therefore, there is no teaching or motivation to combine Goldman with Waggoner and with Potter. As discussed herein, the combined references do not teach or suggest a method for comparing protein compositions between at least two different samples using a set of matched luminescent dyes. Applicants respectfully request that the rejection of claims 6 and 16 under 35 U.S.C. § 103(a) be withdrawn.

Goldman, Waggoner, and Anderson

Claims 7-12 and 17-21 stand rejected under 35 U.S.C. § 103(a) as being obvious over Goldman in view of Waggoner and further in view of Anderson et al., "The TYCHO System for Computer Analysis of Two-Dimensional Gel Electrophoresis Patterns," *Clin. Chem*, 1981, 27(11), 1807-1820 ("Anderson"). Applicants traverse this rejection for the reasons set forth herein.

Anderson discloses a computer method for analyzing images developed from a two-dimensional electrophoresis gel. However, as discussed herein, there is no teaching or motivation to combine the teachings of the Goldman reference with those of the Waggoner reference to give the methods of the subject application. Therefore, there is no teaching or motivation to combine Goldman with Waggoner and with Anderson. As discussed herein, the combined references do not teach or suggest a method for comparing protein compositions between at least two different samples using a set of matched luminescent dyes and even if combined, they would not result in the subject matter recited in the claims of the present application. Applicants respectfully request that the rejection of claims 7-12 and 17-21 under 35 U.S.C. § 103(a) be withdrawn.

Related Applications

Applicants remind the Examiner that she was responsible for the examination of Application Serial No. 09/370,743, which issued as U.S. Patent No. 6,426,190 and is currently responsible for the examination of co-pending Application Serial No. 10/137,180, which is a division of the 09/370,743 application. The present application is a division of the 10/137,180 application. All three have the same disclosure and all claim priority from U.S. Application Serial No. 08/425,480, filed April 20, 1995 which issued as U.S. Patent No. 6,127,134. The Waggoner patent cited herein and other Waggoner patents identified in the Information Disclosure Statement submitted previously have been considered previously by the Examiner and other Examiners. Examiner Cook acknowledged in the Office Actions mailed May 8, 2006

and February 27, 2007 in co-pending application 10/137,180 that "Waggoner differs from the instant invention in not specifically teaching the combination of two different luminescent dyes to form a matched set, wherein the net charge, ionic characteristics and pH characteristics of the combined dyes are matched."

A Supplemental Information Disclosure Statement is provided on every date herewith to bring to the Examiner's attention the references she already cited in co-pending application 10/137,180.

At page 10 of the current Action, the Examiner cited two references as pertinent to applicant's disclosure. Reference B is U.S. Patent No. 6,043,025 which is a division of application serial no. 08/425,480. As stated above, the present application claims priority from the 08/425,480 application. Therefore, U.S. Patent No. 6,043,025 is not prior art relative to the present application.

Reference A, Toda et al., was published on 28 April 1995. A copy of the cover page of the Journal of Chromatography is enclosed herewith. The present application claims priority to an application filed on 20 April 1995. Therefore, the Toda et al. article is not prior art to the pending claims.

CONCLUSION

Applicants submit that claims 1-22 of the subject application recite novel and non-obvious methods of comparing protein compositions between at least two different samples using a set of matched luminescent dyes. In view of the Remarks submitted herein, Applicants respectfully submit that all claims in the subject application are in condition for allowance. Accordingly, reconsideration and allowance of all pending claims are earnestly solicited.

If the undersigned can be of assistance to the Examiner in addressing issues to advance the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,

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